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(54) **Automated isolate extraction using solid phase sorbent.**

(57) A method and apparatus for extracting an isolate from a liquid sample using a solid-phase sorbent contained in a column selectively connected with a positive-displacement pumping means through a narrow tubing coil, the steps of:

(1) drawing said liquid sample by said pumping means into said tubing coil,

(2) introducing said liquid sample by said pumping means into said column wherein said isolate is extracted on said solid-phase sorbent,

(3) washing said solid-phase sorbent by introducing with said pumping means said wash solvent to displace said sample liquid from said column, and

(4) introducing by said pumping means an eluting solvent into said column to remove said isolate and to pass said eluting solvent containing said isolate out of said column.

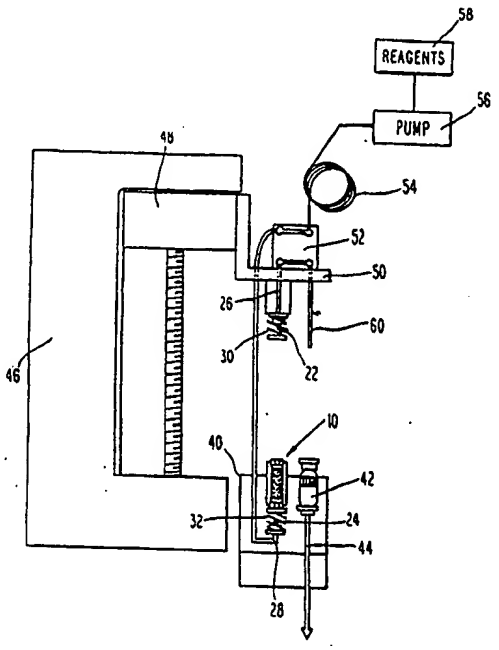

Fig. 1

EP 0 416 326 A2

AUTOMATED ISOLATE EXTRACTION USING SOLID-PHASE SORBENT

Background of the Invention

This invention relates to the extraction of an isolate from a liquid sample using a solid-phase sorbent.

The use of solid-phase sorbents, e.g., bonded silica, to extract an isolate, usually a chemical compound dissolved or otherwise dispersed in a liquid sample, is known. See "Sorbent Extraction Technology" published in 1985 by Analytichem International Inc., Harbor City, CA 90710, and "Baker-10 SPE Applications Guide Vol. 1" published in 1982 by J.T. Baker Chemical Co., Phillipsburg, NJ 08865. It is also known to use disposable columns containing the sorbent between layers or discs of porous frit.

A problem with prepared, disposable columns filled with particulate sorbent between frit layers is the tendency of the packing to settle and form voids which, even when extremely small, can seriously distort the results of extraction and/or elution of the isolate. Radial compression techniques have been used to combat this problem. Rainin Instrument Co. provides packed columns with "Dynamax End-Fittings" which have a threaded axial compression nut that can be turned down prior to use to compress the frit layers and sorbent particles to eliminate voids. Such an end fitting does not lend itself to void elimination by simple axial compression of the end fittings.

It is known to introduce the liquid sample into the column from the top and to draw it down into the column by vacuum, gravity or air displacement systems. Such methods are dependent upon column back pressure and are hindered somewhat by tightly packed columns. It has also been found that such methods can cause channeling of the liquid through the sorbent. When channeling occurs the liquid sample is unevenly passed through the sorbent bed and extraction can be variable and inefficient. This is especially noticeable when the packing density varies from column to column.

Summary of the Invention

It has been found in accordance with this invention that extraction of an isolate from a liquid sample using a solid-phase sorbent in a column can be carried out more easily and accurately using a positive-displacement pump to force the liquids through the column. It has also been found that a column cartridge having end caps compressible by axial pressure applied through engageable liquid conduits can avoid packing voids and lend itself to automated processes. This invention is more particularly pointed out in the appended claims and is illustrated in its specific embodiments in the accompanying drawings.

Brief Description of Drawings

FIG. 1 is a schematic view of an extraction apparatus of this invention.

FIG. 2 is a sectional view of a column cartridge of this invention.

FIG. 3 is a partial sectional view of a column cartridge with an alternative end cap structure.

FIGS. 4,5,6 and 7 are partial schematic views of an apparatus of this invention arranged to carry out the steps of conditioning, Sample loading, washing and elution, respectively.

FIG. 8 is a partial sectional view of a particular needle washing and waste drain assembly.

FIG. 9 and 10 are partial sectional views of a particular sampling tip washing apparatus.

Detailed Description of the Invention

Referring now to the drawings, a cartridge column 10 is shown in FIG. 2 as having a glass column 12 packed with solid-phase sorbent 14 between two layers of frit 16. The frit permits the free passage of liquid but is rigid enough to provide a layer at each end to contain the sorbent 14. One can also use a screen or sieve instead of a frit layer.

At either end of the cartridge is an end cap 18, preferably made of a suitably inert material. The end caps in FIG. 2 are shown to have upper and lower, tapered female fittings 20 adapted to receive male sampling tips 22 and 24 on the liquid conduits 26 and 28. Both male sampling tips 22 and 24 are shown to be spring-loaded to provide for clamping, axial-pressure engagement to effect a seal at each end of cartridge column 10 and also provide for the force of the compressed springs 30 and 32 to assist in disengagement. The spring also accommodates a variety of column lengths. The end caps in FIG. 2 are shown in a tightly compressed position.

FIG 3 illustrates an alternative and preferred face-seal structure of the end cap 18A wherein o-ring washer 34 is provided to engage o-ring groove 36 in liquid conduit face 38 to effect a clamping, axial-pressure sealing engagement and easy disengagement with a liquid conduits 26 and 28. The end cap in FIG. 3 is shown with space 39 to permit the end cap to be compressed further to eliminate

voids. It is also possible to use a flat gasket in place of an o-ring seal or to construct the entire end cap of a suitably compliant seal materials

The apparatus includes a base holder 40 for retaining the cartridge column 10 and sample vial 42 with a waste drain 44. The base can contain a suitable temperature control means (not shown) for the cartridge and the sample. By controlling temperature, one can either maintain or change the efficiency of the separation; i.e., the equilibrium between the solid support and the liquid phase can be regulated. Suitable temperature controls are known in the art, e.g., water circulation thermostatically controlled. An elevator 46 has a carriage 48 which can be moved up and down. The arrangement of the cartridge and the sampling tips 22 and 24 is such that the movement of carriage 48 will engage and disengage conduits 26 and 28 with cartridge 10. Arm 50 on the carriage has the conduit 26 attached to the bottom and carries two-position four-port valve 52. Connected to one port of the valve 52 is a narrow tube coil 54 whose internal volume is about the same size as the desired liquid sample to be drawn from sample vial 42.

A positive-displacement, variable flow-rate pump 56 is connected to coil 54. A suitable type of pump is one that can compress a cylinder of liquid out through coil 54 or can, by reverse pumping, withdraw liquid from coil 54 up into the pumping cylinder (not shown). A suitable pump is a syringe pump, e.g., such as commercially available from Hamilton Instrument Co.

A source of reagents 58 is attached to the pump. Included reagents therein are, for example, water, conditioning agent, e.g., methyl alcohol or acetonitrile, and wash solvent, e.g., deionized water, pH buffer solution, or appropriate organic solvent mixtures. The connection (not shown) between reagents 58 and pump 56 is such that the pump can be alternatively connected to a source of different reagents. This is easily accomplished by means well known in the art.

The carriage arm 50 can be lowered such that the upper and lower sampling tips 22 and 24 engage female fittings 20 in cartridge 10 and are compressed into sealing engagement against springs 30 and 32. The compressive, clamping force will also compress end caps 18 against frit layers 16 to remove any void above packing 14. If sample vial 42 is present on base 40, it will be penetrated by hollow needle 60 and will be located over waste drain 44 as in FIG. 4. In the valve 52 position shown in FIG. 4, coil 54 is connected to conduit 28 and conduit 26 is connected to needle 60.

As shown in FIG. 4, liquid conditioning agent, e.g., methanol, can be pumped from reagents 58 through coil 56 and valve 52 into conduit 28 into the base of the column of cartridge 10. Mixtures of agents may be used and different agents may be used consecutively to achieve the desired conditioning. The agent flows upwardly under the pressure of pump 56 through valve 52 and out through the needle 60 into waste drain 44, sample vial 42 having been removed. The conditioning agent carries out the function "solvation" as described in the Analytichem publication and the J.T. Baker publication referred to hereinabove. When the sorbent is, for example, a bonded silica, formed by the reaction of organosilanes with activated silica, solvation with a conditioning agent like methanol activates and wets the functional end groups on the sorbent surface and positions and enables them to extract isolate molecules from the sample liquid. The sorbents, eluting agents, conditioning agents and isolate compounds of the aforementioned publications and teachings in connection therewith are incorporated herein by reference.

After a suitable amount of conditioning agent is passed out through the column, the pump can be switched to a source of water (or another conditioning agent) to displace the bulk of the conditioning agent but not to disturb the activated sorbent surface. The water goes out through needle 60 and waste drain 44.

Next, a suitable amount of wash solvent is pumped from reagents 58 through the column 10 displacing the bulk of the water and passes out through needle 60 and waste drain 44. The wash solvent is the same as that to be used subsequently after sample extraction. At this point, the entire system from the pump to the needle is filled with wash solvent at the time that pump 56 is turned off.

The next step is to rotate valve 52 to the position shown in FIG. 5. Reverse pumping of pump 56 withdraws a suitable amount of sample liquid from vial 42 through penetrated needle 60 up into tubing coil 54. An alternative way of introducing a sample into the system is to have a sample source among the reagents 58 and to withdraw the sample by pump 56 in the same way as previously described for reagents. The amount of sample liquid withdrawn should just about fill coil 54. Because of the narrow diameter of the coil, there will be little mixing of the sample with residual wash solvent in the system. Introduction of a small air gap above the sample level will help prevent mixing.

The valve 52 is turned to the position in FIG. 6 and vial 42 is removed. The pump then forces the liquid sample in the coil 54 out into the base of column 10 by pumping wash solvent from reagents 58 behind it. The rate of pumping is carefully controlled to achieve the optimum amount of con-

tact with the sorbent to extract the isolate thereon. Next a wash solvent is pumped at a controlled rate through the column 10. The solvent is carefully selected to displace the sample liquid from coil 54 onto the column thus removing the weakly retained impurities from the sorbent without removing the isolate. Such solvent selection is within the skill of the art. The wash solvent also serves to flush out the system including the needle. Both the sample liquid and the wash solvent many be passed to Waste. However, in some cases, the isolate may be the undesired material and the isolate-free solvent liquid may be the desired material which can be recovered at that point.

It is also possible in accordance with the above procedures to load more than one sample of the same or different composition either before washing or with intermittent washing.

The final step is to arrange the apparatus as shown in FIG. 5 and to pump an appropriate eluting solvent, e.g., methanol, from reagents 58 into the column 10 at a controlled rate and amount under optimum conditions to dissolve and remove the isolate from the sorbent. The isolate-containing elution solvent can be collected in sample vial 42. More than one vial may be used consecutively to collect the sample. Optionally, the eluting solvent may be changed to elute a separate fraction of isolate from the sorbent into a separate vial. Means for automatically rotating consecutive vials under the needle may be used. It may be desirable to send the contents to an appropriate analytical device, e.g., a gas or liquid chromatograph (not shown).

In some cases it is desirable that both the exterior and interior surface of the hollow needle 60 be washed after or before the extraction process. For such a step, the sample vial 42, and usually the cartridge 10, are removed from the apparatus of FIG. 1. Referring to FIG. 8, the assembly has a construction wherein the needle 60 is lowered through a conical drain 62 down into the bottom of tubular insert 63. The tubular insert is located inside the hollow waste drain 44 and has a pair of overflow ports 64 located near its top. During washing, two-position four-port valve 52 is turned to the position shown in FIG. 5 which connects the needle 60 to the source of reagents 58 through pump 56 and coil 54. Sample vial 42, of course, is absent and the needle is inserted as shown in FIG. 8.

The appropriate reagent, e.g., water or wash solvent, is pumped through the needle into tubular insert 63 and flows up and around the exterior of the needle 60 and out through ports 64 down through drain 44. This effectively washes both the interior and the exterior of the needle free of any prior samples or contaminants which must be removed prior to future extraction processes. Dimensions of the needle 60, tubular insert 63 and waste drain 44 are selected to afford good flow action for washing without unduly restricting fluid flow. The wash assembly can be disassembled for easy cleaning.

The geometry of column 10 can be important. Longer columns may provide better separation while wider columns provide larger sample capacity. Maintaining uniform column length may provide uniformity of results by controlling the linear velocity of elution. Vial size cartridges may contain as much as 500 mg of packing sorbent.

While the sorbent particles ordinarily act to physically adsorb or absorb the isolate, it is to be understood that sorbent particles may be used that chemically react with the sample to bond or retain the isolate which is to be removed.

The column may be of glass, medical-grade polypropylene, fluorocarbon polymer or other suitable material. The frit can be of inert materials such as fluorocarbon polymer, polyethylene, or stainless steel.

The use of a positive displacement pumping system allows for accurately controlled flow rates through the packed bed as well as enhanced ability to control the actual volume of eluent dispensed in the final analysis vial. Variable flow rate control is important in optimizing separations when changing from one type of separation to another. High pressures provided by this pumping system can allow the use of smaller diameter packing materials with a corresponding increase in resolution between analytes.

The method and apparatus of this invention affords the use of automated systems of extraction and analysis. Cartridges and vials may be fed by automated means, e.g., on rotating trays, to the apparatus. Computerization of the various steps in the process is also possible for optimum operation.

In some cases it is desirable that the interior surfaces of the sampling tips 22 and 24 and connection conduits be washed after or before the extraction process. For such a step, referring to FIG. 9, a wash cartridge 65 would replace cartridge 10 and sample vial 42 would be removed Referring to FIG. 10, during washing, the upper sampling tip 22 would be lowered such that the sampling tips 22 and 24 would pass through duckbill 66. At this point, wash fluid would be pumped through in the same manner as described for FIG. 4.

Claims

1. Method of extracting an isolate from a liquid sample using a solid-phase sorbent contained in a column selectively connected with a positive-displacement pumping means through a narrow tubing

coil, comprising the steps of:

(1) drawing said liquid sample by said pumping means into said tubing coil,

(2) introducing said liquid sample by said pumping means into said column wherein said isolate is extracted on said solid-phase sorbent,

(3) washing said solid-phase sorbent by introducing with said pumping means said wash solvent to displace said sample liquid from said column, and

(4) introducing by said pumping means an eluting solvent into said column to remove said isolate and to pass said eluting solvent containing said isolate out of said column.

2. The method of claim 1 including the steps of introducing by said pumping means a liquid conditioning agent for said solid-phase sorbent into said column, and introducing by said pumping means a wash solvent into said column to displace the liquid conditioning agent from said column.

3. The method of claim 1 wherein said conditioning agent, wash solvent, liquid sample and eluting solvent are each introduced into the base of said column.

4. The method of claim 1 wherein said eluting solvent dissolves a portion of said isolate leaving an undissolved portion on said solid-phase sorbent.

5. The method of claim 4 wherein a second eluting solvent is introduced into said column to dissolve said undissolved portion and to pass said first eluting solvent out of said column.

6. The method of claim 2 wherein the wash solvent in step (3) is the same as that used to displace said liquid conditioning agent.

7. The method of claim 1 wherein the volume of said liquid sample in step (1) is approximately the same as the volume of said narrow tubing coil.

8. The method of claim 2 wherein introducing said conditioning agent is followed by introducing water into said column to displace said conditioning agent.

9. The method of claim 1 wherein step (2) of introducing said liquid sample into said column is by said pumping means forcing said liquid sample out of said coil by wash solvent.

10. Apparatus for extracting an isolate from a liquid sample using a solid-phase sorbent contained in a column connectable to a positive-displacement pumping means,

means for drawing such liquid sample into said apparatus,

two-position selective valve means connected to said tubing coil, which in a first position connects said tubing coil to the base of said column, and which in a second position connects said tubing coil with said sample drawing means.

11. Apparatus for extracting an isolate from a liquid sample using a solid-phase sorbent contained in a column selectively connectable to a positive-displacement pumping means through a narrow tubing coil,

means for drawing said liquid sample by said pumping means into said tubing coil,

means for introducing said liquid sample by said pumping means into said column,

means for introducing by said pumping means wash solvent into said column to displace said sample liquid from said column, and

means for introducing by said pumping means an eluting solvent into said column and for removing said eluting solvent from said column.

12. The apparatus of claim 11 including means for introducing by said pumping means a conditioning agent for said solid-phase sorbent into said column, and means for introducing by said pumping means a wash solvent into said column to displace said conditioning agent from said column.

13. The apparatus defined in claim 12 wherein each of said means for introducing said conditioning agent, wash solvent, liquid sample and eluting solvent are means for introducing into the base of said column.

14. The apparatus defined in claim 10 or 11 wherein said column is contained in a cartridge having end caps with pressure-sealing means adapted to engage and disengage conduits to said pumping means.

15. The apparatus of claim 10 or 11 wherein said means for drawing the liquid sample includes a needle for insertion into said sample.

16. The apparatus of claim 15 including means for passing wash solvent through the interior and over the exterior of said needle.

17. The apparatus of claim 15 including an engageable tubular insert having overflow ports, into which insert said needle may be inserted and in which wash solvent may be passed through said needle into said tubular insert, along the exterior of said needle and out through said overflow ports.

18. A solid-phase extraction cartridge comprising a column containing solid-phase sorbent particles with a porous separation layer above and below said sorbent particles, an end cap above and below said separtion layers with an aperture therein permitting liquid to pass through, said end caps having sealing means adapted to engage and disengage conduits for said liquid, said end caps further being compressible into said column to eliminate significant voids between said separation layers upon the application of axial pressure through said conduits.

19. The cartridge defined in claim 18 wherein the end caps are made of a suitably chemically inert polymer, preferably a fluorocarbon polymer.

20. The cartridge defined in claims 18 or 19 wherein the column consists of glass or a suitably chemically inert polymer.

21. The cartridge defined in claim 18 wherein said porous separation layer is a layer of frit or a screen or a sieve.

22. The cartridge defined in claim 14 or 18 wherein the sealing means are provided with luer fittings or a face seal or a core seal.

23. The cartridge defined in claim 18 wherein the end cap sealing means include o-ring washers.

24. The cartridge defined in claim 18 wherein the frit comprises fluorocarbon polymer particles.

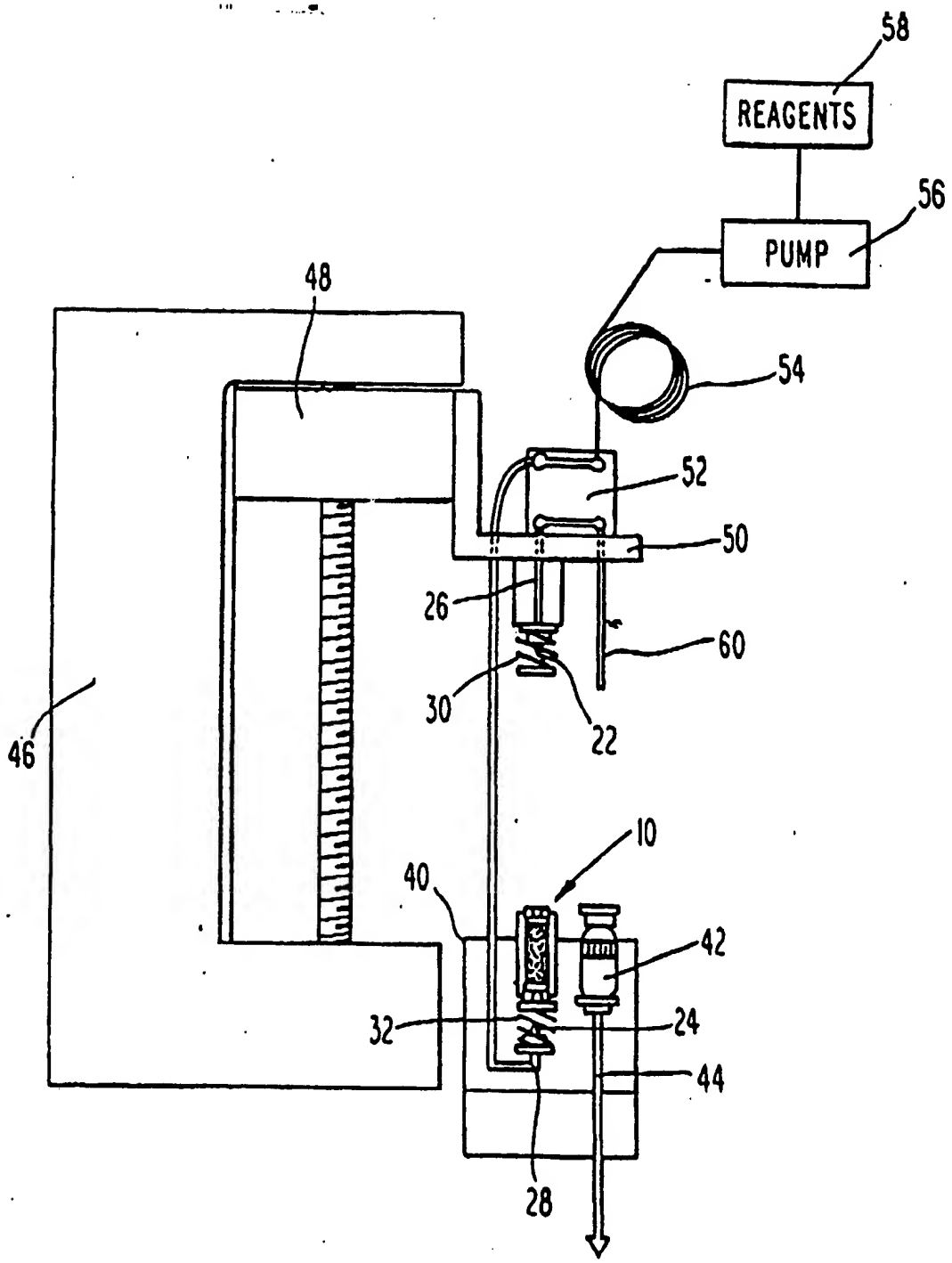

Fig. 1

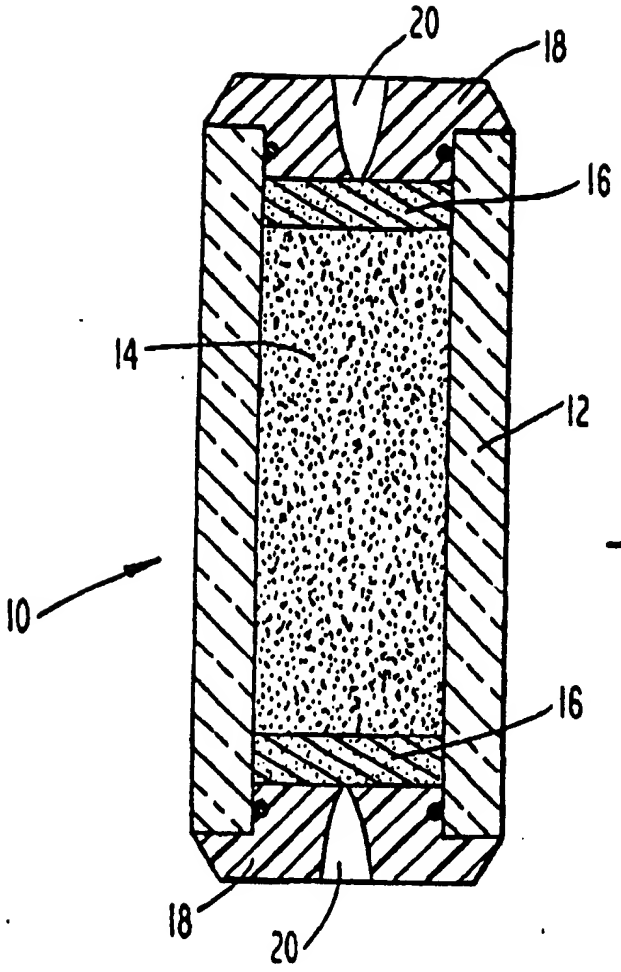

Fig. 2

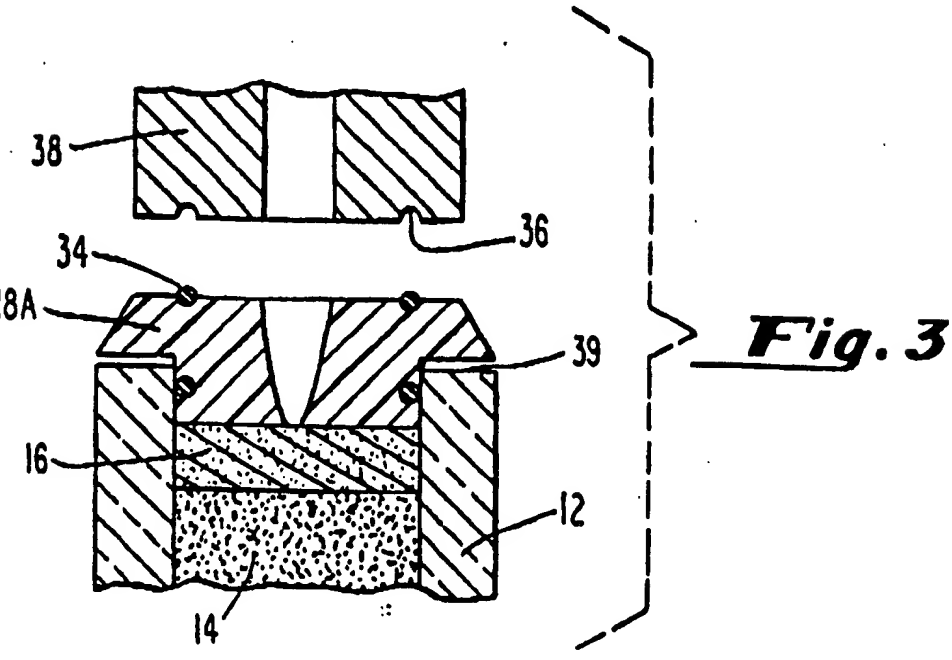

Fig. 3

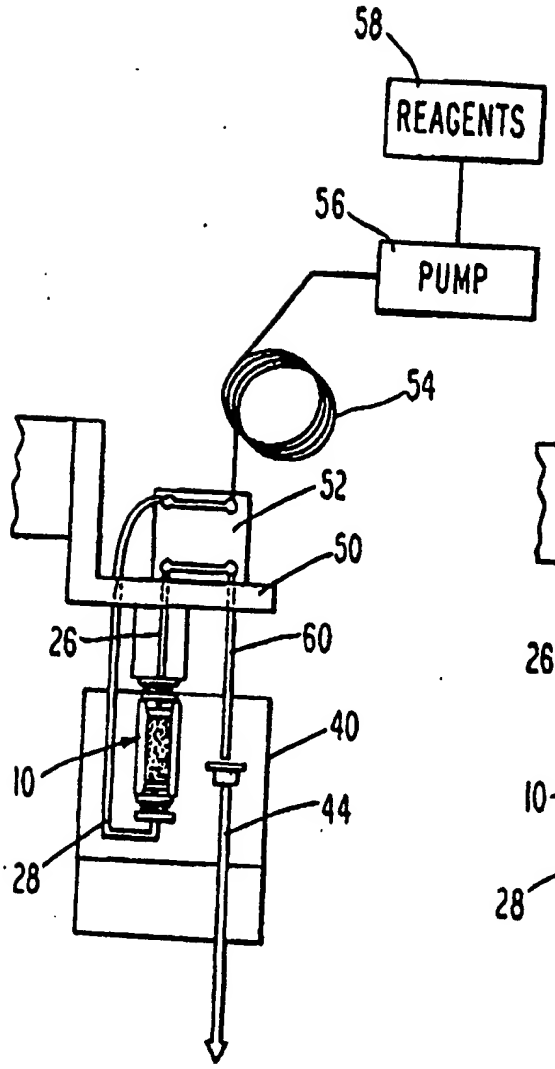
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Fig. 4

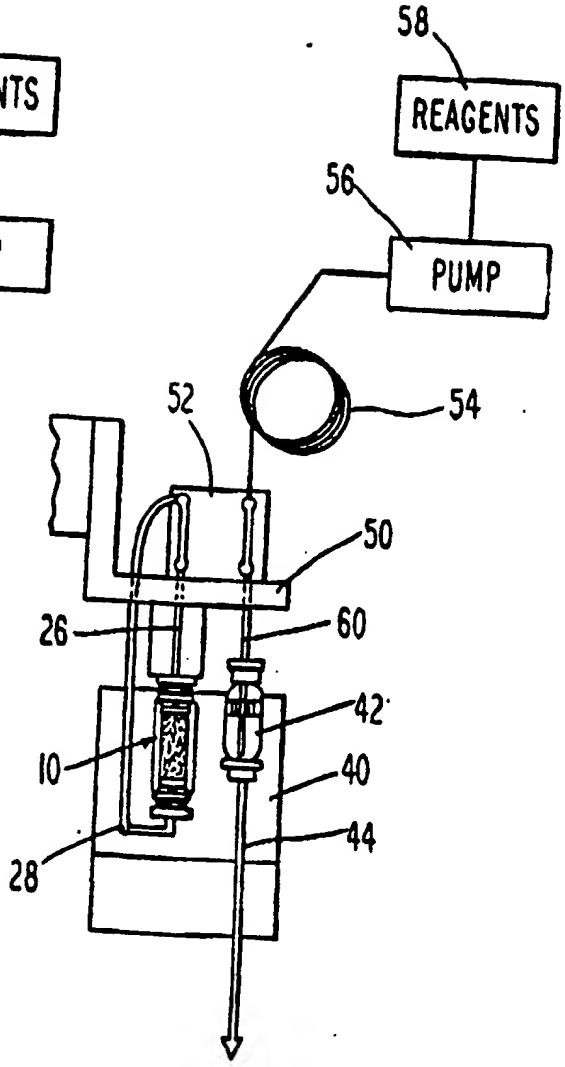
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Fig. 5

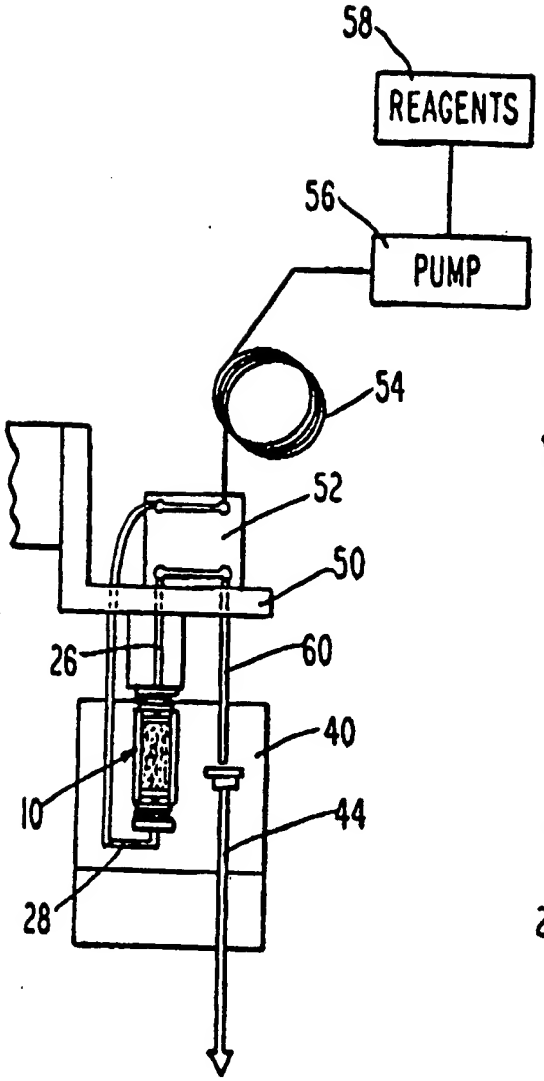
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Fig. 6

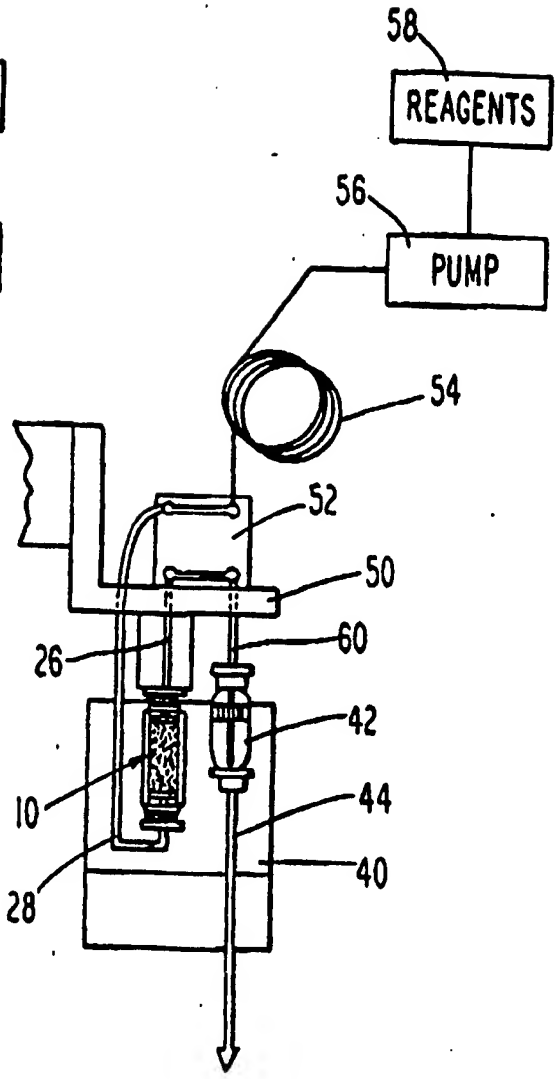
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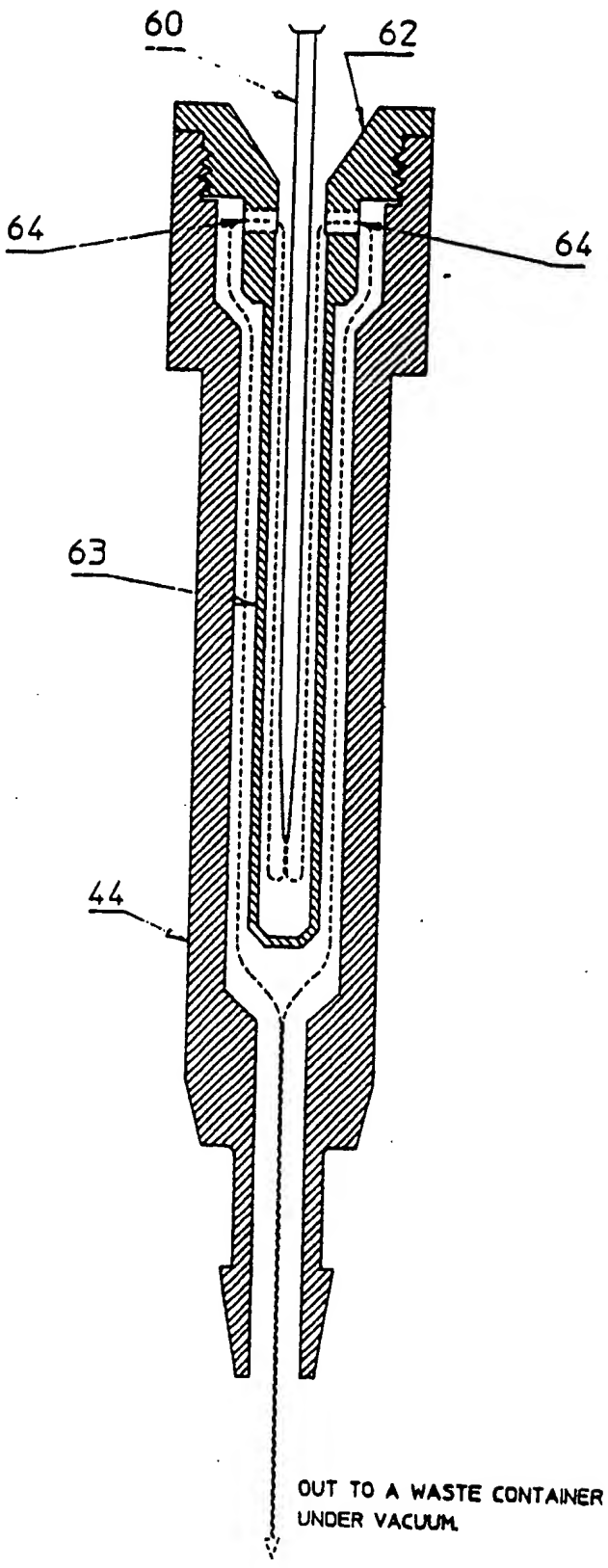
Fig. 7

FIG. 8



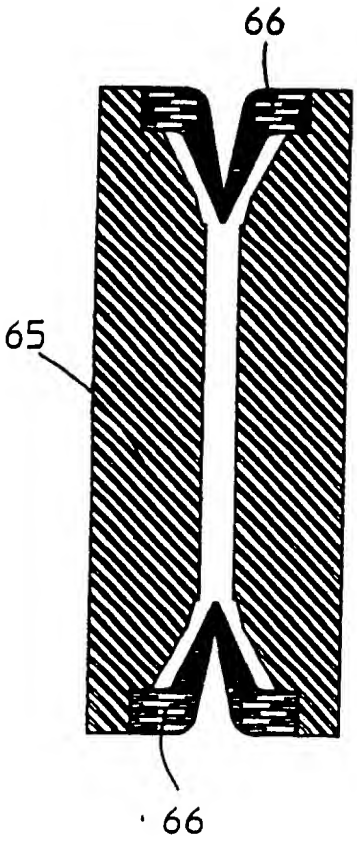


FIG. 9

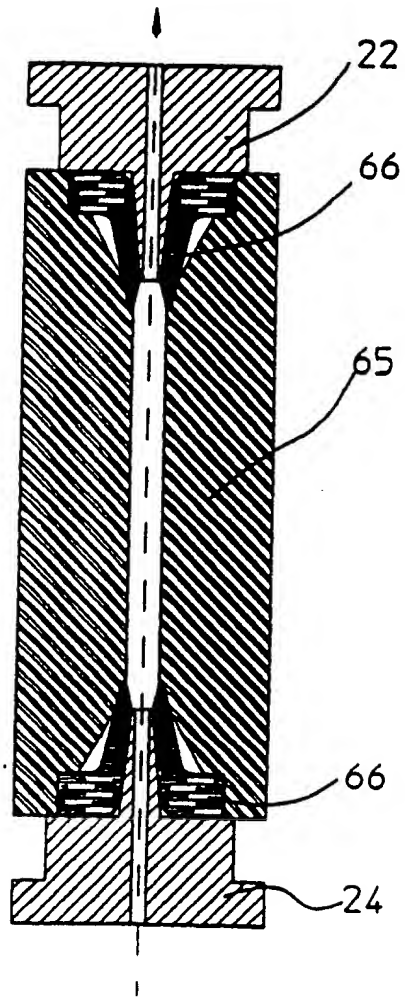


FIG. 10

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(54) **Automated isolate extraction using solid phase sorbent.**

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(2) introducing said liquid sample by said pumping means into said column wherein said isolate is extracted on said solid-phase sorbent,

(3) washing said solid-phase sorbent by introducing with said pumping means said wash solvent to displace said sample liquid from said column, and

(4) introducing by said pumping means an eluting solvent into said column to remove said isolate and to pass said eluting solvent containing said isolate out of said column.

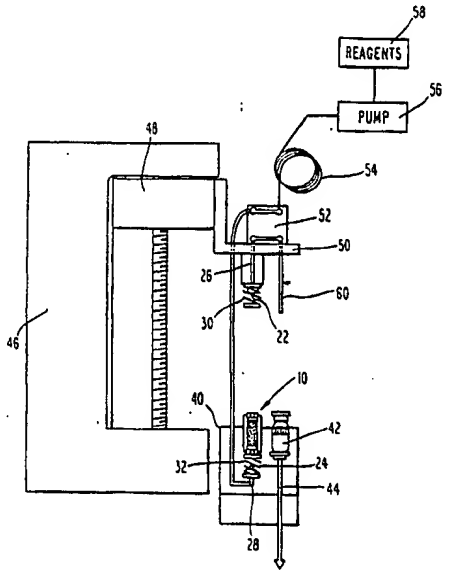

Fig. 1

EP 0 416 326 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 11 5462

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	DE-A-3 002 996 (ROTH) * Page 4, line 1 - page 8 * ---	1,9,10, 11	B 01 D 15/00 G 01 N 30/24 G 01 N 30/60
A	US-A-4 347 131 (BROWNLEE) * Column 3, line 35 - column 4, line 7 * ---	1,10,11	
A	US-A-3 915 642 (SMALL) * Column 3, line 60 - column 6, line 20 * ---	1,2,10, 11,12	
A	US-A-4 094 196 (FRISWELL) * Column 5, line 31 - column 6, line 68 * ---	1,10,11 ,15,16	
A	US-A-4 836 038 (BALDWYN) ---		
Y	EP-A-0 305 817 (MERCK PATENT GES.) * Page 3, column 3, line 10 - column 4, line 23 * ---	18,19, 21,22	
A		20	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
Y	US-A-4 283 280 (BROWNLEE) * Column 3, line 11 - column 5, line 60 * ---	18,19, 21,22	B 01 D G 01 N
A		23	
A	GB-A-2 115 716 (BROWNLEE) * Page 1, line 129 - page 2, line 36 * ---	18	
A	GB-A-2 162 489 (BIO-RAD LABOR.) * Page 2, line 85 - page 3, line 6 * --- -/-	18,19	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	12-02-1991	WENDLING J.P.

EPO FORM 1503 03.82 (P0401)

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

European Patent Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid.

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

X LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.

namely:

See sheet -B-

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid,

namely claims:

☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims,

namely claims:

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 11 5462

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 266 542 (LABOMATIC) * Column 8, line 30 - column 9, line 52 * ---	18	
A	EP-A-0 068 343 (CESKOSLOVENSKA AKADAMIE) * Page 8, line 30 - page 9, line 16 * ---	18,19, 20,21	
A	CH-A- 509 591 (DUTLER) ---		
A	FR-A-2 162 494 (MERCK PATENT) -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	12-02-1991	WENDLING J.P.

EPO FORM 1503 03.82 (P0401)

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims 1-17: Method of extracting an isolate from a liquid using solid phase sorbent.

2. Claims 18-24: A solid phase extraction cartridge.